AMENDMENTS

In the Specification:

Please amend the specification as indicated below. Within each paragraph in which one or more amendments are desired, a ~~strikethrough~~ is provided for deleted matter while underlining is provided for added matter.

Please amend the paragraph appearing on page 3, beginning at line 3, as follows:

Solution-based formulations of IL-4R suffer from ~~other~~ drawbacks ~~be~~ other than those associated with solution phase instability. First, solution-based formulations take up more room and require more care than solid formulations and[,] thus[,] are more costly. Moreover, in general, they must be refrigerated (typically maintained in an environment of 2 to 8°C) which further restricts the storage and transport options. In addition, many solution-based formulations exhibit a protein concentration loss over time, which is presumably due to the formation of dimers and other protein aggregates in solution. Such formulations frequently must be supplemented with stabilizing additives such as buffers and/or antioxidants to minimize solution instability. Thus, it would be desirable to provide a solid or powder-based composition of IL-4R, particularly one that could not only be stably prepared and stored, but additionally administered in solid form, such as an inhaleable dry powder. Many preclinical and clinical studies with inhaled proteins, peptides, DNA and small molecules have demonstrated efficacy both within the lungs and systemically.

Please amend the paragraph appearing on page 3, beginning at line 17, as follows:

Powder formulations represent an alternative to solution formulations, and proteins, when desired in powder form, are most often prepared as lyophilizates (e.g., U.S. Patent No. 5,856,296). Unfortunately, lyophilized powders are typically formed as cakes, which require additional grinding and milling[,] and optionally sieving processing steps to provide flowing powders. In the past few years, spray drying has been employed as an alternative approach for preparing a number of therapeutic protein-based powders, particularly for aerosolized administration (e.g., International Patent Publication Nos.

WO 96/32149; WO 95/31479; WO 97/41833, assigned to Inhale Therapeutic Systems, Inc.). Unfortunately, certain proteins, and cytokines in particular, are prone to degradation during spray drying and loss of their secondary structure (Maa, Y.F., *et al.*, *J. Pharm. Sciences*, **87** (2), 152-159 (1998)). For a representative cytokine, human growth hormone, Mumenthaler reported that spray drying at 90°C resulted in 4% formation of insoluble aggregates and 21% formation of soluble aggregates - a loss of 25% intact protein (*Pharmaceutical Res.*, **11**, 12-20 (1994)). The instability of the illustrative cytokine, hGH, was further demonstrated by Maa, Y.F., et al., *ibid*, who reported 42% aggregate formation (soluble and insoluble) upon atomization of a solution of hGH.

Please amend the paragraph appearing on page 5, beginning at line 16, as follows:

The ~~IL-4~~ IL-4R powder composition, demonstrating insignificant degradation upon preparation and storage, may be prepared in the absence of stabilizing additives or excipients, or may further include a pharmaceutically acceptable excipient. Preferred excipients include zinc salts, citrate, leucine, and combinations thereof.

Please amend the paragraph appearing on page 6, beginning at line 12, as follows:

Also encompassed by the invention is an aerosolized ~~IL4R~~ IL-4R powder formulation, and an ~~IL-4~~ IL-4Rpowder in a unit dosage form.

Please amend the paragraph appearing on page 7, beginning at line 23, as follows:

In the context of the present invention, "IL-4R" and ~~"sIL-4R"~~ "sIL-4R" refer to the extracellular domain of the cell-bound protein that acts as receptor for the cytokine, interleukin-4. As discussed below, IL-4R as used herein is not limited to a single peptide sequence, but is meant to encompass any known protein having IL-4R activity, including naturally and synthetically derived IL-4R as well as agonists and analogs thereof, to the extent that they retain the therapeutic activity associated with native peptide.

Please amend the paragraph appearing on page 8, beginning at line 5, as follows:

As used herein, the term "analog" refers to those compounds in which one or more amino acids have been substituted, deleted (i.e., fragments), added, or otherwise modified from the native (wild-type) human sequence, and which exhibits at least about 10, 20, 30, or 40%, and preferably at least 50%, 60%, or 70%, and most preferably at least 80%, 90%, 95%, 100% or greater than 100% bioactivity of that of the native (non-synthetic), endogenous peptide. The receptor specificity is optionally substantially similar to the native (wild-type), endogenous peptide. Typically, the receptor affinity will be at least 30%, 40%, or 50% that of the native (wild-type), endogenous peptide; more preferably at least 60%, 70%, 80%, 90%, 95%, 100% or greater than 100%.

Please amend the paragraph appearing on page 11, beginning at line 21, as follows:

"Amino Acid" refers to any compound containing both an amino group and a carboxylic acid group, and ~~icnludes~~ includes pharmaceutically acceptable salts thereof. Although the amino group most commonly occurs at the position adjacent to the carboxy function, the amino group may be positioned at any location within the molecule. The amino acid may also contain additional functional groups, such as amino, thio, carboxyl, carboxamide, imidazole, etc. The amino acids may be synthetic or naturally occurring and may be used in either their racemic or optically active (D-, or L-) forms, for example, as a single optically active enantiomer or as any combination or ratio of enantiomers.

Please amend the paragraph appearing on page 12, beginning at line 26, as follows:

A "minimal change" when used in reference to IL-4R monomer content in a spray dried IL-4R powder refers to a ~~chance~~ change (i.e., decrease) in monomer content of no more than about 10% in comparison to the level of IL-4R monomer in the corresponding pre-spray dried solution or suspension.

Please amend the heading appearing on page 13, line 7, as follows:

Components Of The Respirable IL-4R ~~powder~~ Powder Composition

Please amend the paragraph appearing on page 13, beginning at line 17, as follows

The compositions of the present invention are particularly effective for the treatment of allergic diseases and ~~condition~~ conditions, such as asthma and atopic dermatitis. Moreover, the spray dried IL-4R powder containing compositions described herein are ~~surprising~~ surprisingly stable (i.e., exhibit minimal chemical and physical degradation upon preparation and storage, even under extreme conditions of temperature and humidity). That is to say, the powders provided herein are surprisingly robust, even in the absence of stabilizing or dispersibility enhancing excipients. The IL-4R powders of the invention (i) are readily dispersed by aerosol delivery devices (i.e., demonstrate good aerosol performance), (ii) exhibit surprisingly good physical and chemical stability during powder manufacture and processing, and upon storage, and (iii) are reproducibly prepared (Examples 1-5).

Please amend the paragraph appearing on page 14, beginning at line 3, as follows:

IL-4R for use in the invention is generally characterized as follows. Endogenous mature interleukin-4 receptor is expressed as a 140kDA membrane glycoprotein that binds IL-4 with high affinity (Idzerda RL et al., 1990 *J. Exp. Med.*, 171 (3), 861-873; Jacobs, CA et al. 1991, *Blood*, 77(11):2396-2403, both of which are incorporated by reference herein). The extracellular domain of human IL-4R, cloned and produced in CHO cells in serum containing media, is a highly glycosylated (N-linked) and sialylated protein having a nonglycosylated molecular weight of 23.9 kDa and containing 209 amino acid residues. The extracellular domain IL-4R is located between residues 24 and 234 of the mature interleukin-4 receptor. Mass spectrometry data shows the protein molecular weight to be about 37kDa, suggesting at least 35% glycosylation. By SDS-PAGE analysis, the protein elutes as a 54 kDa band. The pI of IL-4R is 3.36 to 5.18 as determined by isoelectric focusing. The unfolding transition temperature as determined by DSC is 57.8°C and the unfolding process is highly reversible.

Please amend the paragraph appearing on page 16, beginning at line 21, as follows:

However, preferred excipients will, in part, serve to improve one or more of the following: the aerosol properties of the composition, its chemical stability, its physical stability, and/or storage stability. Preferred excipients may also function to provide more efficient and reproducible delivery of IL-4R by dry powder inhaler, and additionally improve the handling characteristics of the ~~Il-4R~~ IL-4R powder composition (e.g., flowability and consistency) to facilitate manufacturing and powder filling.

Please amend the paragraph appearing on page 16, beginning at line 27, as follows:

In particular, the excipient materials can often function to improve the physical and chemical stability of the respirable ~~Il-4R~~ IL-4R powder composition or active agents contained therein. For example, the excipient may minimize the residual moisture content and hinder moisture uptake and/or enhance particle size, degree of aggregation, surface properties (i.e., rugosity), ease of inhalation, and targeting of the resultant particles to the lung. The excipient(s) may also simply serve simply as bulking agents for reducing the active agent concentration in the dry powder composition.

Please amend the paragraph appearing on page 17, beginning at line 22, as follows:

Exemplary polypeptide and protein excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, hemoglobin, and the like. Particularly preferred are dispersibility enhancing ~~prolypeptides~~ polypeptides, e.g., HSA, as described in ~~international~~ International Publication No. WO 96/32096, assigned to Inhale Therapeutic Systems, Inc., the contents of which are incorporated by reference herein.

Please amend the paragraph appearing on page 17, beginning at line 28, as follows:

Representative amino acid/polypeptide components, which may also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, tyrosine, tryptophan, and the like. Preferred are amino acids and ~~peptide~~ peptides that function as dispersing agents. Amino acids falling into this categoray include

hydrophobic amino acids such as leucine (leu), valine (val), isoleucine (isoleu), tryptophan (try) alinine (ala), methionine (met), phenylalanine (phe), tyrosine ~~(try)~~ (tyr), ~~histidin~~ histidine (his), and proline (pro). One particularly preferred amino acid is the amino acid leucine. Leucine, when use in the formulations described herein includes D-leucine, L-leucine, and racemic leucine. Dispersibility enhancing peptides for use in the invention include dimers, trimers, tetramers, and pentamers composed of hydrophobic amino acid components such as those described above. Examples include di-leucine, di-valine, di-isoleucine, di-tryptophan, di-alanine, and the like, tripleucine, tripvaline, tripisoleucine, triptryptophan etc.; mixed di- and tri-peptides, such as leu-val, isoleu-leu, try-ala, leu-try, etc., and leu-val-leu, val-isoleu-try, ala-leu-val, and the like and homo-tetramers or pentamers such as tetra-alanine and penta-alanine. Particularly preferred oligopeptide excipients are dimers and trimers composed of ~~2~~ two or more leucine residues, as described in Inhale Therapeutic Systems Inc. International Patent Application PCT/US00/09785 entitled, "Dry Powder Compositions Having Improved Dispersibity. Of these, dileucine and trileucine are particularly preferred.

Please amend the paragraph appearing on page 18, beginning at line 27, as follows:

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as ~~fructerse~~ fructose, maltose, galactose, glucose, d-mannose, sorbose, and the like; disaccharides, such as raffinose, melezitose, maltodestrins, dextrans, straches and the like;~~a nd~~ and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbital (glucito), myoinasitol and the like.

Please amend the paragraph appearing on page 19, beginning at line 6, as follows:

Additionally, the respirable IL-4R composition of the invention may include polymeric excipients/additives such as polyvinylpyrrolidones, derivatized celluloses ~~suchas~~ such as hydroxypropylmethylcellulose, Ficcols (a ~~polyeric~~ polymeric Sugar), hydroxyethylsartch, dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin), polyethylene glycols, pectin flavoring agents, salts (e.g., sodium chloride), antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates such as "TWEEN 20" and "TWEEN 80"), lecithin, oleic

acid, benzalkonium chloride, ~~sorbittan~~ sorbitan esters, lipids (e.g., phospholipids, fatty acids), steroids (e.g. cholesterol) and chelating agents (e.g., EDTA). For compositions containing a polymeric component, the polymer is ~~may~~ typically present to a limited extent in the composition, i.e., at levels less than about 10% by weight. Preferred compositions of the invention are those in which the IL-4R is preferably non-liposomally or polymer encapsulated~~,or~~ , or non-coated (i.e., absent a discrete coating layer). Preferred IL-4R compositions such as those exemplified herein are immediate-acting formulations, i.e., designed for immediate rather than for sustained release applications.

Please amend the paragraph appearing on page 19, beginning at line 21, as follows:

Other pharmaceutical excipients and/or additives suitable for use in the respirable IL-4R compositions according to the invention are listed in "Remington: the Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), and in "The Handbook of Pharmaceutical Excipients", 3rd Edition, A. H. Kibbe, ed., American Pharmaceutical Association, Pharmaceutical Press, 2000, the disclosures of which are herein incorporated by reference.

Please amend the paragraph appearing on page 20, beginning at line 11, as follows:

To prepare an IL-4R solution for spray-drying, ~~Il-4R~~ IL-4R (and any other exipients) is generally dissolved in water, optionally containing a physiologically acceptable buffer. The pH range of solution is generally between about 3 and 10, which nearer neutral pHs being preferred, since such pHs may aid in maintaining the physiological compatibility of the powder after dissolution of powder within the lung. The aqueous formulation may optionally contain additional water-miscible solvents, such as acetone, alcohols and the like. Representative alcohols are lower alcohols such as methanol, ethanol, propanol, isopropanol, and the like. The solutions will generally contain IL-4R dissolved at a concentration from 0.01% (weight/volume) to about 20% (weight/volume), preferably from 0.1% to 10% (weight/volume), more preferably 1% to 3% (weight/volume). Alternatively, components of the IL-4R formulation may be spray-dried using an organic solvent or co-solvent system, employing one or more solvents such as acetone, alcohols

(e.g., methanol and ethanol), ethers, aldehydes, hydrocarbons, ketones and polar aprotic solvents.

Please amend the paragraph appearing on page 21, beginning at line 15, as follows:

In some instances, it may be desirable to provide the respirable IL-4R dry powder formulation in a form that possesses improved handling/processing ~~characteristics~~ characteristics, e.g., reduced static, better flowability, low caking and the like, by preparing compositions composed of fine particle aggregates, that is, aggregates or agglomerates of the above-described respirable IL-4R. Dry powder particles, where the aggregates are readily broken back down to the fine powder components for pulmonary delivery, as described, e.g., in Johnson, K., et al., ~~U.S.~~ U.S. Patent No. 5,654,007, 1997, incorporated herein by reference. Alternatively, the respirable IL-4R powders may be prepared by agglomerating the powder components, sieving the materials to obtain the agglomerates, spheronizing to provide a more spherical agglomerate, and sizing to obtain a uniformly-sized product, as described, e.g., ~~and~~ in Ahlneck, C., et al. International PCT Publication No. WO 95/09616 (1995), incorporated herein by reference.

Please amend the paragraph appearing on page 23, beginning at line 12, as follows:

The spray dried respirable IL-4R powder compositions of the present invention are further characterized as having an essentially unchanged monomer content as compared to that of its pre-spray dried solution or suspension. In other words, the spray drying process does not induce the formation of dimers or other aggregates, thereby affecting the percent monomer in the composition. That is to say, the change in monomer content between spray dried powder and pre-spray dried solution or suspension is "essentially unchanged", e.g., the percentage of monomer content of spray dried powder as compared to that of the pre-spray dried solution or suspension is preferably no more than about 15%, more preferably no more than about 10%, more preferably no more than about 7%, even more preferably about 5% or less, as exemplified by the representative ~~IL-4~~ IL-4R powders described in the Examples.

Please amend the paragraph appearing on page 25, beginning at line 10, as follows:

Other dry powder dispersion devices for pulmonary administration of dry powders include those described, for example, in Newell, R.E. et al., European Patent No. EP 129985, (1988); in Hodson, P.D. et al., European Patent No. EP 472598, (1996); in Cocozza, S., et al., European Patent No. EP 467172, (1994), and in Lloyd, L.J. et al., U.S. Patent No. 5,522,385, (1996). Also suitable for delivering the ~~Il-4R~~ IL-4R powder compositions of the invention are inhalation devices such as the Astra-Draco "TURBUHALER". This type of device is described in detail in Virtanen, R., U.S. Patent No. 4,668, 218); in Wetterlin, K. et al., U.S. Patent No. 4,667,668, (1987); and in Wetterlin K., et al., U.S. Patent No. 4,805,811, (1989). Also suitable are devices which employ the use of a piston to provide air for either entraining powdered medicament, lifting medicament from a carrier screen by passing air through the screen, or mixing air with powder medicament in a mixing chamber with subsequent introduction of the powder to the patient through the mouthpiece of the device, such as described in Mulhauser, P., et al., U.S. Patent No. 5,388,572, (1997).

Please amend the material appearing on page 27, line 10, as follows:

Recombinant Human ~~Il-4R (rhuIl-4R)~~ IL-4R (rhuIL-4R) (Immunex Corporation, Seattle, WA)

Please amend the paragraph appearing on page 28, beginning at line 24, as follows:

Storage stable spray-dried powders of the interleukin receptor protein, ~~Il4-R~~ IL-4R, having superior aerosol properties and further characterized by superior chemical and physical stabilities were prepared. Powders were prepared in both the presence and absence of excipients; excipients employed were from a variety of representative chemical classes (e.g., organic acid salts, amino acids, metal cations). The ~~Il-4~~ IL-4R powders are stable upon long-term storage and are resistance to extreme conditions of temperature and humidity.

Please amend the paragraph appearing on page 28, beginning at line 31, as follows:

Representative ~~Il-4R~~ IL-4R powders were prepared according to the following protocols.

Please amend the paragraph appearing on page 29, beginning at line 9, as follows:

Dry powder compositions of IL-4R were formulated in deionized water with zinc chloride for spray-drying. 600-700 mg batches of a 5.4:1 $ZnCl_2$: ~~Il-4R formulation~~ IL-4R formulations were prepared by dispensing 19.53 mL of IL-4R Solution A and 0.456 mL of a 19.37 mg/mL solution of $ZnCl_2$ into a 50 mL volumetric flask and adjusting the final volume to 50 mL by addition of deionized water. The final concentration of phosphate buffer was 1.9 mM.

Please amend the paragraph appearing on page 29, beginning at line 16, as follows:

Dry powder compositions of IL-4R were formulated in deionized water containing a citrate salt for spray-drying. 600-700 mg batches of citrate: ~~Il-4R~~ IL-4R formulations were prepared by combining approximately 12 mL of Solution A and 200 mg of citrate in solution at pH 7.5 and adjusting to a final volume of 50 mL by addition of deionized water. The final concentration of phosphate buffer was 1.2 mM.

Please amend the paragraph appearing on page 29, beginning at line 23, as follows:

Dry powder compositions of IL-4R were formulated in deionized water containing leucine for spray-drying. 600-700 mg batches of the leucine: IL-4R ~~formulation~~ formulations were prepared by combining approximately 12 mL of Solution A and 200 mg of leucine and adjusting to a final volume of 50 mL by addition of deionized water. The final concentration of phosphate buffer was 1.2 mM and the pH was 7.5.

Please amend the paragraph appearing on page 30, beginning at line 6, as follows:

Additional powder formulations contemplated include IL-4R formulations, both neat and excipient containing, prepared using a citrate buffered or a water-based (no buffer) IL-4R solution. Preferred IL-4R powders in accordance with the invention comprise, in addition to IL-4R , one or more of the following excipients: trileucine, raffinose, mannitol, sucrose, F-68, divalent metal cations such as magnesium, calcium, and the like, glucophosphate, zinc salts, trehalose, glycine and histidine. Specific

formulations may comprise from 10-40 weight % trileucine, or 1% by weight F-68, or 10% by weight citrate, or 3:1 to 10:1 by weight cationic divalent metal cation: IL-4R, or 10-30% by weight sucrose, or 5-50% by weight trehalose, or any combination of the above. Additional illustrative ~~Il-4R~~ IL-4R formulations include those containing both citrate and leucine (e.g., a formulation with a citrate: leucine: IL-4R ratio of 15:15:70) or raffinose (e.g., formulations comprising 5% - 50% raffinose).

Please amend the paragraph on page 31, beginning at line 18, as follows:

Bulk powder was weighed into borosilicate glass vials in a glove box. For 0% relative humidity (RH) stability samples, vials were capped, placed into a foil overwrap pouch containing desiccant and heat-sealed before storing in temperature chambers. For humidity controlled stability samples, vials were left open and stored in desiccators at 25°C. Samples were pulled and analyzed by UV, SDS-PAGE, SE-HPLC and SEM after 2 weeks.

Please amend the paragraph appearing on page 33, beginning at line 6, as follows:

The emitted dose was measured by collecting the aerosol on a glass fiber filter placed in a holder over the mouthpiece of the chamber of the device. To measure the emitted dose percent (ED%), a blister pack was dispersed as an aerosol using a dry powder inhaler as described above. The powder sample was collected ~~ona~~ on a pre-weighed glass fiber filter (Gelman, 47mm diameter). The aerosol cloud was collected onto the filter from the chamber by drawing at an airflow rate of 30 ± 0.5 L/min for 2.5-3.5 seconds. An automatic timer controlled the duration of the draw. The sampling pattern simulates a patient's slow deep inspiration.

Please amend the paragraph appearing on page 34, beginning at line 13, as follows:

The aerosol performance of the IL-4R powder formulations was quite good, all having ~~Ed~~ ED values of essentially 60% or greater and MMAD values of 4μm or less, with at least 34% or particle having MMADs of less than 3.3 μm.

Please amend the paragraph appearing on page 35, beginning at line 14, as follows:

The effects of temperature and relative humidity for representative ~~IL-4~~ IL-4R formulations was determined. Of the illustrative ~~IL-4~~ IL-4R powders prepared, the leucine spray dried powder appeared to be the least morphologically stable, based upon temperature and RH-driven changes in morphology. No significant morphology changes were noted in any of the other powders when exposed to identical storage conditions.

Please amend the paragraph appearing on page 36, beginning at line 3, as follows:

Thus, the spray dried powders of the invention exhibit glass transition temperatures that are much higher than room temperature, a preferred characteristic of dry powder formulations, particularly for long-term storage. Thus, in another aspect, the representative IL-4R ~~powder s~~ powders of the invention are characterized by Tgs that are higher than 100°C. Due to the high Tgs of the powders of the invention, these ~~IL-4~~ IL-4R powders can be stably stored at temperatures in excess of ambient or 25°C, and can be stably stored at 30°C, 35°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C or greater (up to about 100°C or even more) for extended periods of time (e.g., one week, two weeks, one month, two months, three to six months, nine months, up to a year or longer), whilst maintaining their advantageous aerosol characteristics (exhibiting essentially minimal drop in emitted dose, of no more than about 15%, preferably no more than about 10%, and even more preferably no more than about 5%, and essentially no change in MMAD, as characterized by an increase in MMAD of no more than about 1micron, and preferably no more than about 0.75 microns, and even more preferably no more than about 0.5 microns, upon storage).

Please amend the paragraph appearing on page 36, beginning at line 18, as follows:

Dielectric Relazation Spectrometry (DRS): Sine the glass transition temperature (Tg) of the ~~IL-R-4R~~ IL-4R spray dried formulations could not be determined by DSC, DRS was performed. Two DRS experiments were conducted on the zinc containing IL-4R formulation, Formulation 1(B), to better identify the glass transition temperature of a representative formulation. The first experiment conducted was a standard DRS analysis (TA Instruments Dieletctic Analyzer (DEA 2970)), run at 2°C/min from 30°C to 150°C

and cooled to 30°C again, scanning through frequencies of 1, 10, 100, 10^3, and 10^4 and 10^5 Hz. The second experiment conducted was a softening experiment much like a thermal mechanical analyzer (TMA) run at 2°C/min from 30°C to 250°C and scanning through frequencies of 1, 10, 100, 10^3, and 10^4 and 10^5 Hz. Both experiments were run on the Zn:IL-4R powder as is (Formulation 1(B)) and after drying overnight at 100°C (Formulation1(B)-(D)).

Please amend the paragraph appearing on page 37, line 4, as follows:

Thermo mechanical Anaysis (TMA): The TMA experiments were performed by monitoring sample thickness during a DRS experiment. The same electrode configuration was used as in the first experiment, except the gasket was removed. The ram force was set at 20N and the thickness of the sample and the temperature were recorded manually every couple of minutes from 30°C to 250°C. The onset of softening is at 224°C for both Formulation 1(B) and Formulation 1(B)-D. The softening seen in the TMA experiments is due to degradation and a possibility of a glass transition happening simultaneously. Since there is no other softening happening at lower temperatures, the 1Hz peaks from the standard DRS tests are due to another mechanism such as the onset of side chain motions or ion conduction and not due ~~t oa~~ to a glass transition (Seyler, R.J., 1994, "Assignment of the Glass Transition", *ASTM*, 108-113). If the glass transition happens simultaneously with the decomposition, then in the sample with the lower 1Hz loss factor peak may have the glass transition shifted to a lower temperature as well. Since the standard DEA test was only run to 150°C, it is clear that there is no glass transition below 150°C. Evaluation of the permitivity versus temperature plots confirmed the standard s-shaped profiles expected for this type of analysis.

Please amend the paragraph appearing on page 39, beginning at line 3, as follows:

Based on results obtained from the powder stability temperature data at two weeks, as the storage temperature increased, the amount of monomer content compared to the initial time data decreased. The largest ~~changed~~ change in percentage monomer from initial was at 50°C with a range of 2.1%, in the neat formulation, to 1.9% in both the zinc and citrate formulations. In the 2 week powder stability humidity study, the citrate

formulations exhibited the largest drop of just 1.8% in monomer from initial at the extreme RH of 75%. This was probably due to citrate crystallization. Thus, the IL-4R compositions of the invention exhibit essentially no thermal degradation upon spray-drying (as evidenced by monomer content of the illustrative compositions), and exhibit a minimal decrease in monomer upon storage, under a variety of illustrative temperature and humidity conditions. Unlike other proteins, which upon spray drying are often prone to significant aggregation (Maa, Y.F., et al., ~~et al.,~~ J. of Pharmaceutical Sciences, Vol 87 (2), p. 152-159 (1997)), IL-4R has been found to be surprisingly resistant and impervious to such conditions, and forms spray-dried powders in which the protein exhibits insignificant degradation even in the absence of commonly-employed stabilizing/protecting excipients.

Please amend the paragraph appearing on page 40, beginning at line 7, as follows:

UV spectrophotometric analyses were used to evaluate turbidity (i.e., aggregation/precipitation) in reconstituted samples. Measurements were performed on a Hitachi U-3000, dual beam spectrophotometer. Instrument parameters were set at a scan rate of 300nm/min; 1.0nm slit width; and a scan ranged from 450nm to 200nm. Samples were visually inspected for particulate matter. Insoluble aggregates were determined quantitatively by measuring the turbidity of the solution with UV. Linear regression to correct for scatter was performed from absorbance values at 350, 375 and 400nm. Absorbance at λ_{max} corrected for light scattering was extrapolated from the equation for the regression line. The percent insoluble aggregate is the percentage of absorbance corrected for light scattering, divided by absorbance uncorrected at λmax as shown in Eq. 1 below.

Please amend the paragraph appearing on page 40, beginning at line 24, as follows:

Samples were either reconstituted or diluted to a concentration of 0.1 mg of ~~IL-4R~~ IL-4R peptide/mL with water prior to analysis.

Please amend the paragraph appearing on page 42, beginning at line 1, as follows:

There were no changes in the gel profiles between the formulated solutions before spray drying and the reconstituted aerosol drug powders. ~~the~~ The monomer bands of all samples and controls of IL-4R on the gels ran at higher molecular weight (approx. 50kDa) than reported values and appear broad and diffuse. This is most likely attributed to the protein being a glycoslyated and affecting the migration of IL-4R through the gel. There was another distinct band running at approximately 97 kDa, this was attributed to the dimer which is presumably the dimer form of the protein. Several lower molecular weight banks were visible in the 5μg load gel that have not been identified.

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